PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 06259PC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/01257	International filing date *(day/month/year)* 28.03.2003	Priority date *(day/month/year)* 28.03.2002
International Patent Classification (IPC) or both national classification and IPC C12N15/11		
Applicant THE GENETICS COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.10.2003	26.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Barnas, C Telephone No. +49 89 2399-7469

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/01257

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-42 as originally filed

Sequence listings part of the description, Pages

1-14 as originally filed

Claims, Numbers

1-25 received on 02.06.2004 with letter of 02.06.2004

Drawings, Sheets

1-6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 15, 20, 22

   because:

   ☒ the said international application, or the said claims Nos. 15, 20, 22 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	22-25
Industrial applicability (IA)	Yes:	Claims	1-14, 16-19, 21, 23-25
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 15, 20, 22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of said claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV

Lack of unity of invention

The present application contains two separate groups of inventions that are not so linked as to form a single general inventive concept. The two inventions are:

1. An isolated protein as described in claim 1 and associated subject matter and methods involving the nucleic acid SEQ ID NO: 1, and the protein SEQ ID NO: 2 as described in claims 2-5, 9, 13 (complete); 10-12, 15-19 (part).

2. Methods involving an ELP protein as described in claims 6-8, 14, 20-25 (complete); 10-12, 15-19 (part).

The common concept linking together the two groups of inventions is a protein. Since proteins are known the above listed separate groups of inventions are not so linked as to form a single general inventive concept and the present application, therefore, lacks unity (Rule 13.1 PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The documents mentioned in the present Written Opinion / International Preliminary Examination Report are numbered as in the International Search Report. D1 corresponds to the first document of the Search Report, D2 to the second document etc.

The document/s/ D8 was/were not cited in the international search report. A copy/Copies of the document/s/ is/are appended hereto.

D8: Eichenmuller et al: 'The human EMAP-like protein-70 (ELP70) is a microtubule destabilizer that localizes to the mitotic apparatus' Journal of Biological Chemistry, vol. 277. no. 2, January 11, 2002, pages 1301-1309

1. The term "ELP protein" or "human ELP protein" as used in claims 6, 8, 14-16, 20, 22, 25 embraces the human ELP protein disclosed in D8. The subject matter of claims 22-25 would be provided by the skilled person, according to the circumstances, using routine procedures starting from D8 without the exercise of inventive skill. **Claims 22-25** are, therefore, not inventive.

2. D2 represents the closest prior art for group 1 of inventions. Said document discloses the nucleotide sequence and protein sequence of a new member (epsin 4) of the epsin family. The difference to the subject matter of claims 1-5, 9 and 13 is the isolation of an additional protein encoded by said nucleic acid and its use for diagnostic purpose. The cited prior art does not contain any indication that would prompt the skilled person to use the gene of D2 for such purposes. Said claims, are, therefore inventive.

3. D8 represents the closest prior art for group 2 of inventions. The difference to the subject matter of claims 6-8, 10-12, 14-21 is the use of the human ELP gene of D8 for diagnostic and medical purposes as described in said claims. The cited prior art does not contain any indication that would prompt the skilled person to use the gene of D8 for such purposes. Said claims, are, therefore formally acknowledged, inventive (see however, paragraph 4).

4. The present application does not provide evidence that the human ELP protein of D8 can be used for methods as described in claims 6-8, 10-12, 14-21. In addition, hyperproliferative diseases associated with the ELP protein of D8, as described in claim

15, have not been disclosed and are not known in the prior art. **Claims 6-8, 10-12, 14-21** are, therefore, not disclosed, contrary to Art. 5 PCT.

Amended claims of PCT Application No. IB03/01257

Claims

1. An isolated protein comprising an ENTH domain and having growth inhibiting activity wherein said protein has an amino acid sequence as set forth in Seq. Id. No. 5.

2. An isolated nucleic acid encoding a protein of claim 1.

3. A vector comprising a nucleic acid as defined in claim 2.

4. A host cell comprising a vector of claim 3.

5. The host cell of claim 4, wherein said cell is an eukaryotic cell.

6. A method for the identification of a hyperproliferative disease, in particular benign and malignant tumors, or a genetic predisposition thereof, which comprises detecting in a body fluid or a tissue sample of a subject a change in the expression level of an ELP protein and/or at least one mutation within a nucleic acid sequence encoding an ELP protein or detecting a rearrangement in the genomic *elp* locus.

7. The method of claim 6 wherein said mutation is located within the DNA region coding for the ENTH domain, in the 5' untranslated region, in a codon encoding an evolutionary conserved amino acid, in the promoter or in a splicing site.

8. The method of claim 6 or 7 wherein said mutation leads to a non-functional ELP protein, to a reduced protein expression or no protein, or a fusion protein.

9. The method of anyone of claims 6 to 8, wherein said nucleic acid sequence encoding an ELP protein is selected from Seq. Id. No. 1 or the nucleic acid sequence as defined in claim 2.

10. The method of anyone of claims 6 to 9, wherein the disease is lung cancer.

Amended claims of PCT Application No. IB03/01257

11. The method of anyone of claims 6 to 9, wherein the disease is kidney cancer.

12. The method of anyone of claims 6 to 9, wherein the disease is stomach cancer.

13. A method for the production of an ELP protein comprising transformation of suitable host cells with a nucleic acid of claim 2 in an expression construct, cultivation of said cells under conditions allowing protein expression of said protein, and isolation of the produced proteins.

14. Use of an antibody capable of binding specifically to an epitope of an ELP protein in a method for the identification of a hyperproliferative disease or a genetic predisposition thereof.

15. Use of a nucleic acid encoding an ELP protein for the gene therapy of a hyperproliferative disease associated with ELP proteins, in particular the nucleic acid sequence set forth in Seq. Id. No. 1 or the nucleic acid sequence as defined in claim 2.

16. A pharmaceutical composition for the treatment of a hyperproliferative disease, in particular benign and malignant tumors, comprising an ELP protein and/or a nucleic acid sequence encoding an ELP protein, in particular a protein as set forth in Seq. Id. No. 2 or Seq. Id. No. 5 and a nucleic acid sequence as set forth in Seq. Id. No. 1 or as defined in claim 3.

17. The pharmaceutical composition of claim 16, wherein the hyperproliferative disease is lung cancer.

18. The pharmaceutical composition of claim 16, wherein the hyperproliferative disease is kidney cancer.

19. The pharmaceutical composition of claim 16, wherein the hyperproliferative disease is stomach cancer.

20. Use of an oligonucleotide which specifically hybridizes to a region of a mRNA encoding an ELP protein for the therapy of hypoproliferative diseases

and/or diseases characterized by incorrect cell differentiation.

21. The use of claim 20, wherein said oligonucleotide comprises chemical modifications.

22. Use of a double stranded RNA (dsRNA) for gene silencing wherein said RNA has a nucleotide sequence which is complementary to an exon region of a gene encoding an ELP protein.

23. The use of claim 22 wherein said RNA has a length of about 200-2000 base pairs, preferably 700-800 base pairs.

24. The use of claim 23 wherein said RNA has a length of about 18-25 base pairs, preferably 20-22 base pairs.

25. The use of claim 22, wherein said ELP protein is human ELP.